REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claims 1, 5 and 13 have been amended to more particularly point out and distinctly claim the composition of this invention, by reciting that the composition is "in a solid dosage form". Support is found at page 5, lines 2-5 of the specification.

Claims 1-20 and 61-82 are pending.

Claims 1-20 and 61-82 are rejected under 35 USC 103 as being unpatentable over Negoro et al. in view of Muller et al. This ground of rejection is respectfully traversed.

(1) First of all, it should be noted that the present invention is characteristic in a pharmaceutical composition comprising as the active ingredient micronized particles of AS-3201 having a mean particle size of less than about 20 μm, preferably of less than about 10 μm, particularly preferably about 0.5 to about 3 μm, in a specific ratio. It is also characteristic in that the micronized particles of AS-3201 with additives in the specified ratios as defined in claims 5, 13, or others.

In view of the characteristic features, the active ingredient exhibits excellent fast-dissolving properties and thereby the pharmaceutical composition can release the active ingredient rapidly.

(2) The Examiner pointed out that the cited Muller et al. US 5,858,410 discloses that the dissolution rate increases as the particles surface area increases in accordance with the Noyes-Whitney law. However, the Muller et al teach a particle in the range of 10 to 1,000 nm (in the Office Action, the Examiner erroneously cited as in range of 10 to 1,0000 nm) (10 to 1,000 nm corresponds to 0.01 to 1 μm). Such a nanometer size is too much small and is not suitable for the purpose of the present invention as is explained hereinafter.

The invention of Muller et al. is concerned with a pharmaceutical nanosuspension which is mainly for the purpose of intravenous administration and for such a purpose the active ingredient shall be such a small size as "nanometer" size. It should also be noted that the preparation of Muller et al. is a suspension, which is clearly different from the pharmaceutical composition in the solid dosage form of the present invention. In order to make clearer, the present claim 1 is again amended

1.5 μm commensurate w/ scope w/ Declaration .5 supported by spec.

Falls within preferred w/in range

Although the Examiner pointed out as "Muller discloses a marked increase in saturation solubility and in turn dissolution with the reduction of particle diameter and increases surface area from microns to nanometers (col. 5, lines 58-60 and col. 7, lines 7-10)" and further as "the reference teaches a particle in the range of 10 to 1,0000 nm (correct, 1,000 nm) and 65% dissolution rate within ten minutes (col. 14, lines 49-55 and figures).", it is not directly concerned with the fast dissolution properties mentioned in the present invention.

That is, as is seen from the description of Muller et al, col. 14, lines 37-41 and 49-53, the test was carried out by introduction of the drug particles into a 0.9% NaCl solution saturated with the drug. That is, the particles of the drug was superfluously dissolved in a solution saturated with the drug. This is essentially different from the dissolution test by Paddle method in the present invention wherein it is tested how the active compound is dissolved out from the solid form of composition.

As is emphasized in our comments to the last Office Action, in the pharmaceutical composition in the solid dosage form (e.g. tablet) of a hardly soluble active compound, there is usually a problem of less dissolution out of the active compound from the composition (e.g. tablet), and hence, it is more important to improve the solubility of the active AS-3201 used in the present invention in order to prepare a pharmaceutical composition having improved dissolving property. Thus, in view of extremely low solubility of the active compound in the present invention, it is absolutely required to take an ingenuity in order to

increase the solubility of the active compound AS-3201.

(3) Since the Examiner said as "Muller discloses that the dissolution rate increases as the particle surface area increases in accordance with the Noyes-Whitney law", and "as a result of increased dissolution rate increases bioavailability", we would like to point out that it has usually been considered that it is not simple and not predictable to increase solubility of a compound by micronization thereof.

Please refer to "Design and Evaluation of Peroral Pharmaceutical Preparations (in Japanese)", edited by Mitsuru Hashida, Yakugyo Jihosya, February 10, 1995, pp. 81-84, 168-171 (cited in the International Search Report of the original PCT/JP98/04658) thereof (which was submitted as SUPPLEMENTAL INFORMATION DISCLOSURE STATMENT on September 26, 2000). A copy of the English translation will be sent again together with a confirmation copy of this letter.

This literature also mentioned as follows:

(i) The Noyes-Whitney's equation predicts that the larger the specific surface area of the drug substance is, the faster the dissolution rate is obtained." (cf. English translation of pp.81-84 passages, page 2, lines 9-8 from the bottom)

(ii) Size reduction by pulverization will increase surface area causing an increase in dissolution rate. In addition, as seen from the Ostwald-Freundlich's equation (Equation 5-8) described in Chapter 5, this results also in an increase in solubility itself. (cf. English translation of pp.168-171 passages, page 1, lines 12-14)

(iii) It has been reported about many insoluble drugs, for example, phenytoin[3], nitrofurantoin[4], benoxaprofen[5], and others[6,7], that size reduction can improve the bioavailability. (cf. English translation of pp.168-171 passages, page 1, lines 18-20)

However, this literature discloses also the following opposite comments.

(A) However, in practice, pulverization alone can not always elevate the dissolution rate. (cf. English translation of pp.81-84 passages, page 3, lines 11-12)

(B) However the size should be of the submicron level or less for a great influence of size reduction to be exerted on solubility[1,2], and therefore pulverization usually made on many drugs may be not very effective in increasing the solubility by size reduction. (cf. English translation of pp.168-171 passages, page 1, lines 14-17)

(C) However, in some cases, the finer the particle is, the more easily flocculation occurs, causing reduction of the surface area in contact with water (effective surface area), and thus the dissolution rate of some drugs is even decreased by pulverization. In particular, hydrophobic drugs are very apt to flocculate. As shown in Fig. 7-2, the dissolution rate of pulverized griseofulvin is slower than that of non-pulverized griseofulvin[9]. (cf. English translation of pp.168-171 passages, page 1, lines 8-3 from the bottom)

(D) Once pulverization equilibrium has been reached, although the particle size will be kept unchanged n continued pulverization, the

mechanical energy applied to particles is consumed for destruction of the crystal structure, and this increases consequently lattic strain and lattice disturbance. This indicates that pulverization not only increases the surface area of particles but also exerts a great influence on the reactivity and stability of the solid; therefor attention should be paid to such mechanochemical changes in the properties when a drug is pulverized. It is often experienced that pulverization makes a drug amorphous. Fig. 7-4 shows that cephalexin, when pulverized by a ball mill, becomes amorphous with decreased degree of crystallinity[12]. Ampicillin also becomes amorphous on pulverization[13]. Fostedil[14] and chloramphenicol palmitate[15] have been found to show transformation to the other crystal form. In these cases the solubility itself will change. In general, solubility increases when the drug has become amorphous but the stability is lowered in most cases, which should be kept in mind. (cf. English translation of pp.168-171 passages, page 2, line 20 to the end line)

(E) Mechanochemical effects, such as heat or mechanical pressure generated during pulverization, are problematic in many cases. (cf. English translation of pp.168-171 passages, page 5, lines 4-5)

Please also be advised that in the cited Muller et al reference, even as to saturation solubility, it is mentioned as "an increase in the saturation solubility when the particle size is decreased is postulated in the Ostwald-Freundlich equation ..., but this does not have an effect on particles in the micrometer range ...." (cf. Muller et al, col. 5, end line - col. 6, line 7)

As is seen from the above, even by decreasing the particle size, it does not necessarily always result in increase of the dissolving rate, and further it is not necessarily predicted whether the drug is well pulverized with keeping the stability of the drug.

Besides, like in griseofulvin, drugs are sometimes flocculated by pulverization, and thereby, the dissolution rate of pulverized product is slower than that of non-pulverized product. Further, some products becomes amorphous by pulverization, which results in significant lowering of the stability of the drug.

(4) The Examiner further pointed out that Negoro et al teach the instantly claimed aldose reductase inhibitor compound in a pharmaceutical composition for the treatment of diabetes and also refer to the composition of Example 29.

As is also recognized by the Examiner, Negoro et al do not specify the particle size of the active compound or the dissolution rate. This Negoro et al do never teach or even suggest to micronize the active compound to the specific range nor the effects of the micronization on the dissolution rate.

In order to prove experimentally that the compound prepared by the method disclosed in the cited Negoro et al reference does not show the desired fast dissolution properties but the specifically micronized

compound of the present invention show the desired superior properties, comparative experimental data are submitted in the form of Declaration. (see attached Declaration by Mr. Mamoru OHASHI)

As is seen from said comparative experiment in Declaration, the compound AS-3201 prepared in a similar manner as described in Example 1 of Negoro et al, USP 5,258,382 had a mean particle size of about 87 μm and the tablets prepared by the thus prepared AS-3201 particles did not show the desired dissolution characteristics, but on the other hand, when micronized AS-3201 having a mean particle size of about 1.5 μm or about 10 μm of the present invention was used, the tablets showed greatly superior dissolution characteristics.

Such excellent characteristics of the present invention would never been predicted from the cited Negoro et al reference even by taking into consideration together with the secondary Muller et al reference (the latter does never teach or even suggest that a pharmaceutical composition in a solid dosage form comprising a specific mean particle size ("micrometer" size, not in "nanometer" size) of the active compound exhibits the desired fast dissolution properties)

Again we would like to emphasize that in view of so low solubility of the active AS-3201 of the present invention. the present inventors have studied means for micronizing AS-3201 crystals suitable for preparing the desired pharmaceutical composition and have found that when the AS-3201 crystals are micronized in a specific particle size, i.e. in a mean particle size of less than 20 μm, preferably less than 10 μm, the active AS-3201 can exhibit excellent solubility. As a result, the present inventors succeeded in preparation of an AS-3201-containing pharmaceutical composition which has extremely improved dissolving properties and superior bioavailability in comparison with a composition prepared by using non-micronized AS-3201 crystals as is clear from comparison of the products of Examples and Reference Examples.

II. Re: Rejection of Claims 61-62 under 35 USC § 103(a) as being unpatentable over Negoro et al (5,258,382) in view of Muller et al (5,858,410) in further view of Schneider et al (5,356,636)

As is explained above, neither the primary Negoro et al reference nor the secondary Muller et al reference do teach or even suggest the specific pharmaceutical composition of the present invention.

The Examiner further pointed out as "Muller et al teach the use of stabilizers to cover the surface of the particles to prevent aggregation (col. 7), further as to another secondary reference, as "Schneider et al teach the instant acids as stabilizers (col. 4, lines 68) in compositions", and then further as "it would have been obvious to one of ordinary skill in the art at the time the invention was made to add the instant acids since Schneider et al teach these acids as stabilizers for the actives."

Firstly, although in the Muller et al, dispersion-stabilizing substances and charge stabilizers are also incorporated in order to prevent aggregation of the particles as shown in claims 12-15 and claims 16-18, which are effective for prevention of aggregation of particles in the

suspension. These substances used in the Muller et al are essentially different from the stabilizer (i.e. acidic substance such as citric acid, tartaric acid, maleic acid, malic acid) of the present inventi n in both of the kinds and the object and effect of use thereof.

Secondly, the invention of Schneider et al reference is concerned with stable dry powders which are insoluble in hot water (and in which one or more fat-soluble vitamins and/or one or more carotenoids are embedded in a gelatin-based matrix), and in case of active substances which are sensitive to oxidation, an antioxidant (e.g. ethoxyquin, BHT, BHA or tocopherol) and a stabilizer (e.g. citric acid, phosphoric acid or phytic acids or salts thereof, etc.) are added. Thus, in Schenider et al reference, the stabilizer is added merely for the purpose of prevention of oxidation of the active compound. Besides, in working examples in Schneider et al. only phytic acid is used.

On the other hand, in the present invention, the specific acidic substance has an acidity more potent than that of AS-3201 and is incorporated for the purpose of prevention of hydrolysis of the active substance due to the moisture absorption during storage, which is clearly distinguished from the cited schneider et al.

Accordingly, we believe that the present invention as claimed in claims 61 and 62 is never taught or even suggested by those cited references even in combination thereof.

In view of the foregoing, it is respectfully submitted that the claims as amended are nonobvious and patentable over the prior art.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version with markings to show changes made**."

Accordingly, reconsideration and allowance is respectfully solicited.

Respectfully submitted,

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